switching to ε because TGF-β1–deficient mice are characterized by dramatically elevated serum IgE concentrations[10]. Shimizu and colleagues now show that treatment of B cells with TGF-β1 induces Id2 expression, thereby down-regulating S_ε germline transcription and switching to ε[3].

These results have exciting implications. The specific functions described for Id2 and TGF-β1 in IgE regulation suggest that defects in these factors may contribute to human diseases characterized by IgE overproduction, a possibility that can be directly tested by genetic analysis. Identification of Id2 as a critical suppressor of ε switch transcription raises the possibility that other genes in activated B cells may be targets of negative regulation by Id2. The demonstration that TGF-β1 induces Id2 expression suggests that this may prove to be a general mechanism for relaying signals by this pleiotropic cytokine. And finally, there may be practical ramifications. Because the negative consequences of IgE production can be so profound, suppression of IgE is an important therapeutic goal, and the specificity with which Id2 regulates ε switching makes Id2 an intriguing target for therapy.

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Novel interferons

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Type I IFNs are important in antiviral immunity. Two studies report the identification of another family of molecules that have similar properties to the type I IFNs but are otherwise structurally and genetically distinct.

Interferons (IFNs) form an important group of cytokines that are best known for their ability to induce cellular resistance to virus infection[1–3]. However, IFNs also affect many other cellular functions, such as cell growth, and they possess immunomodulatory activities. IFNs include the type I IFN family (also termed the IFN-αβ family) and a single member type II or IFN-γ family. In humans, type I IFNs comprise at least 13 functional nonallelic genes encoding IFN-α, one gene encoding IFN-β and the less extensively studied genes encoding IFN-ω, IFN-κ and limitin[4,5]. All type I IFNs bind to the same heterodimeric receptor (IFN-αβR), whereas the IFN-γ protein binds to IFN-γR. The extracellular domains of the IFN-αβR and IFN-γR subunits contain conserved amino acid residues, including several cysteine residues, that are also found in the subunits of the interleukin 10 receptor (IL-10R) and in receptors for the emerging family of IL-10–related proteins, all of which belong to the class II cytokine receptor family[6,7]. In this issue of *Nature Immunology* Sheppard *et al.*[8] and Kotenko *et al.*[9] describe a novel family of cytokines that are structurally related to the type I IFNs and to the IL-10 family. Like other IFNs, the newly described cytokines protect cells from virus infection and induce major histocompatibility complex (MHC) class I antigen expression, suggesting that these previously unknown mediators contribute to the antiviral defenses and perhaps carry out other functions similar to those of the type I and type II IFNs. Although functionally similar to type I IFNs, these cytokines can be viewed as members of a distinct family: the first novel IFN family defined in over 20 years.

The three members of this newly identified cytokine family, termed IFN-λ1, IFN-λ2 and IFN-λ3 by one group[9] and IL-28A, IL-28B and IL-29 by the other[8] (HUGO has tentatively used the interleukin nomenclature), bind to a heterodimeric receptor, in which one subunit is a novel member of the class II cytokine receptor family and the other is identical to the second chain of the IL-10R (**Fig. 1**). These newly described cytokines are functionally similar to the type I IFNs because their synthesis is induced by virus infection or double-stranded RNA, they render cells resistant to virus infection and they activate the same intracellular signaling pathways as type I IFNs. Despite the similarities to type I IFNs, a number of observations indicate that the IFN-λs represent a distinct family. (For simplicity, the terminology proposed by Kotenko *et al.*[9] will be used here.) The sequence similarity of IFN-λ to IFN-α (15–19 % amino acid identity) is significant but lower than among even the most distant members of the type I IFN family. In addition, the genes for all three members of the IFN-λ family are clustered on chromosome 19 (q13.13 region), whereas the genes for all type I IFNs are clustered on human chromosome 9 (the gene encoding IFN-γ is located on chromosome 12). Finally, the IFN-λ genes contain multiple exons, whereas type I IFN genes are encoded within a single exon. As pointed out by Sheppard *et al.*[8], the IFN-λ family represents an interesting evolutionary link between the type I IFNs and the IL-10 family: although IFN-λ proteins are structurally more closely related to the type I IFNs than to IL-10, their genomic structure resembles that of the IL-10 family.

One of the most interesting findings reported by the two groups[8,9] is that all three IFN-λ proteins utilize a heterodimeric class II cytokine receptor composed of the newly identified class II cytokine receptor subunit IFN-λR1 (also termed IL-28Ra[8]) and a second chain, IL-10R2, that also serves as a subunit of the IL-10R and of the receptor for the IL-10–related cytokine IL-22[7]. Promiscuity in the usage of cytokine receptor subunits is a common vice among cytokines: for example, several members of the IL-2 family share the receptor γ-chain and the IL-6 family cytokines share the gp130 subunit[10]. Similar to other class II cytokine receptors, IFN-λR1 appears to determine the specificity of binding and it probably also drives much of the recruitment of intracellular signaling molecules.

Type I and II IFNs and all other known cytokines that utilize class II cytokine receptors signal by activating the Jak tyrosine kinases–signal transducers and activators of transcription

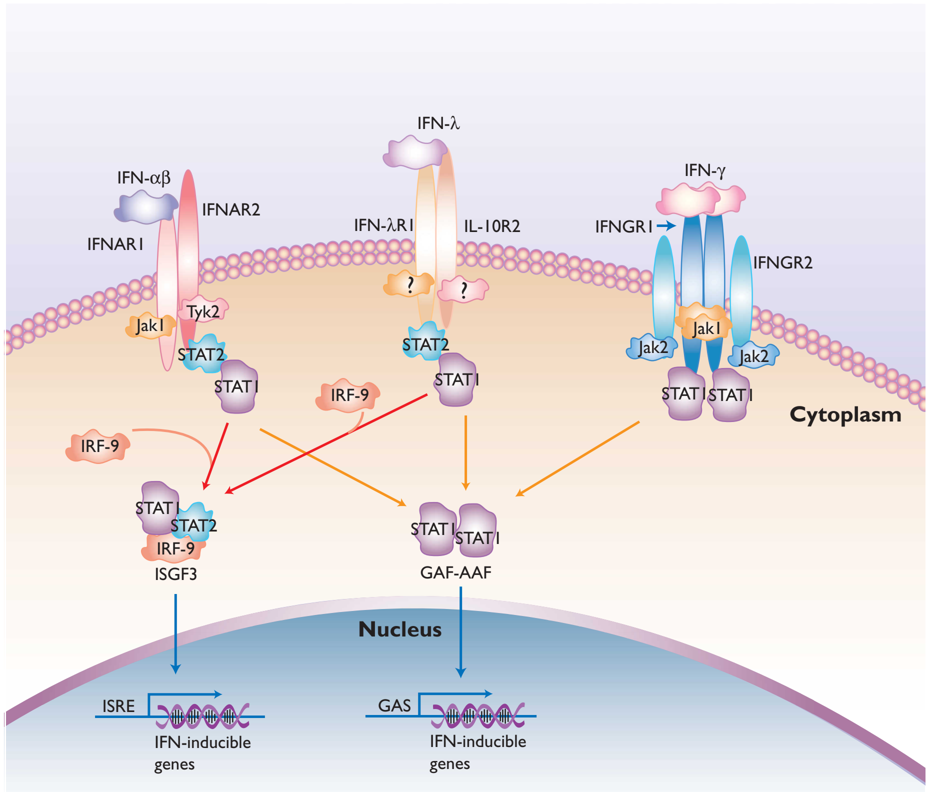

Figure 1. Comparison of signaling pathways activated by IFN-αβ, IFN-γ and the newly described IFN-λ. IFN-αβ (type I IFNs) and IFN-γ (type II IFN) bind to specific and distinct heterodimeric receptors. Binding of IFN-α or IFN-β to their receptor leads to the activation of two receptor-associated tyrosine kinases, Jak1 and Tyk2; this is followed by tyrosine phosphorylation of the STAT1 and STAT2 proteins. Phosphorylated STAT1 and STAT2 combine with IRF-9 (IFN-regulatory factor 9) to form the trimeric ISGF-3 complex, which, upon translocation to the nucleus, binds to the *cis* element ISRE (IFN-stimulated response element), which is present in most IFN-α and IFN-β–responsive genes. In contrast, binding of IFN-γ to its receptor leads to tyrosine phosphorylation of the Jak1 and Jak2 tyrosine kinases, resulting in the phosphorylation of STAT1 but not STAT2. Phosphorylated STAT1 homodimerizes to form the GAF-AAF complex, which translocates to the nucleus and binds to the IFN-γ activation site (GAS) element present in most IFN-γ–inducible genes. Like IFN-γ, IFN-α and IFN-β signaling can also lead to the formation of the GAF-AAF complex and its binding to the GAS regulatory element. The three newly identified IFN-λ proteins (also termed IL-28A, IL-28B and IL-29) bind to a heterodimeric receptor composed of a previously unknown IFN-λR1 subunit and IL-10R2, which also serves as the second chain of the IL-10R. Although the tyrosine kinases activated by IFN-λ have not yet been identified, available evidence indicates that both STAT1 and STAT2 are activated and the downstream signaling pathways activated by IFN-λ appear to be indistinguishable from those activated by IFN-α and IFN-β.

(Jak-STAT) pathway[7,11,12]. Generally, a member of the Jak family of tyrosine kinases (typically Jak1) is associated with the first chain of the receptor (R1) and another Jak kinase family member (for example, Tyk2 or Jak2) is associated with the second chain of the receptor (R2) (**Fig. 1**). Cross-linking of the extracellular domain of the class II cytokine receptors leads to Jak kinase activation with ensuing phosphorylation of the R1 intracellular domain, recruitment of one or two STAT proteins, their tyrosine phosphorylation by the Jak kinases and subsequent translocation to the nucleus. The Jak kinases associated with the IFN-λR have not yet been positively identified, but Jak1 and Tyk2 are likely candidates. What has been shown is that IFN-λR cross-linking leads to both STAT1 and STAT2 activation and resulting formation of the IFN-stimulated regulatory factor 3 (ISGF3) and GAF-AAF complexes (**Fig. 1**). In this respect, downstream IFN-λ signaling is indistinguishable from type I IFN signaling through the IFN-αβR. Interestingly, IFN-λ also produces STAT3 and STAT5 activation, which is more characteristically associated with signaling by IL-10 and IL-10–related cytokines[7,9].

Like other IFNs, IFN-λ proteins induced resistance to virus infection in several human cell lines. IFN-λ also induced two cellular genes that are known to play a role in IFN-induced protection from virus infection, the genes encoding 2′,5′-oligoadenylate synthetase and MX1 (also known as MxA). An important immunoregulatory activity, enhancement of MHC class I antigen expression, was also demonstrated with IFN-λ. Together with the finding that virus infection induces IFN-λ expression, these observations strongly suggest that the IFN-λ system may contribute to resistance to virus infection in the body. However, data from Kotenko *et al*. and Sheppard *et al*. suggest that IFN-λ may have a lower specific activity in some biological assays than IFN-α[8,9]. Thus, a better understanding of the importance of IFN-λ in antiviral resistance and other processes will have to await the outcome of experiments in knockout mice that are likely to be generated in the near future.

IFNs are arguably among the oldest known and most intensely investigated cytokines. Until recently, it seemed that all the important IFN genes and proteins had already been described. The discovery of the IFN-λ family suggests that the search for novel IFNs may not be over yet.

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